Tetrahedron Letters,Vol.29,No.15,pp 1841-1844,1988 0040-4039/88 $3.00 + .00
Printed in Great Britain Pergamon Press plc

REACTION BETWEEN GLYCAL BENZYL ETHERS AND THALLIUM(III) NITRATE. SYNTHESIS OF SHOWDOMYCIN ANALOGUES.

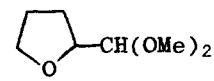
Andrew Kaye[a], Stephen Neidle[b], and Colin B. Reese*[a]

[a]Department of Chemistry, King's College London, Strand, London WC2R 2LS, U.K.
[b]Institute of Cancer Research, Clifton Avenue, Sutton, Surrey SM2 5PX, U.K.

Summary: On treatment with thallium(III) nitrate, trihydrate in acetonitrile solution, 3,4,6-tri-*O*-benzyl-D-glucal (5) gives the ring-contracted aldehyde (6) which has been converted into the showdomycin analogue (8); 2-(α-D-2'-deoxyribofuranosyl)maleimide (12) has similarly been prepared from (10) in satisfactory overall yield.

A number of years ago, McKillop, Taylor and their co-workers reported[1] that, on treatment with thallium(III) nitrate, trihydrate (TTN) in methanol solution, cyclic olefins very readily undergo an oxidative ring contraction reaction. As an example, these workers showed[1] that when 3,4-dihydro-2*H*-pyran (1) was allowed to react with TTN in methanol solution at 60°C for 12 hr, 2-(dimethoxymethyl)tetrahydrofuran (2) was obtained in 65% isolated yield. We have found that (1) was virtually quantitatively converted into (2) in 10 min at room temperature when it was treated with a stoicheiometric quantity of TTN in methanol solution.

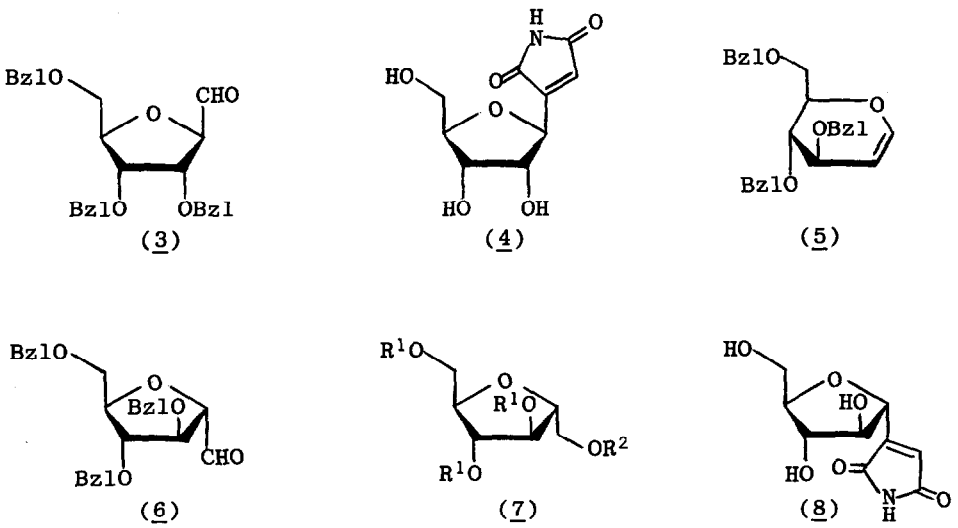
(1)



(2)

Trummlitz and Moffatt have reported[2] an elegant synthesis of the nucleoside antibiotic showdomycin (4), based on 2,5-anhydro-3,4,6-tri-*O*-benzyl-D-allose (3) as the starting material. The fact that the preparation of the latter compound (3) involved[2] seven steps starting from 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose prompted us to investigate the possibility of preparing analogous benzylated anhydro-sugars by reacting the corresponding glycal derivatives with TTN. Treatment of 3,4,6-tri-*O*-benzyl-D-glucal[3] (5) with a stoicheiometric quantity of TTN in acetonitrile solution at room temperature for 1 hr gave what is assumed to be 2,5-anhydro-3,4,6-tri-*O*-benzyl-D-mannose (6) as the main product. When the latter material (6) was allowed to react with sodium borohydride in absolute ethanol, 2,5-anhydro-3,4,6-tri-*O*-benzyl-D-mannitol (7; R^1 = CH_2Ph, R^2 = H) was obtained in 62%

overall yield for the two steps starting from (5). The characterization of this anhydro-mannitol derivative (7; $R^1 = CH_2Ph$, $R^2 = H$) was based on the properties of its crystalline 4-nitrobenzoate ester, m.p. 77°C, and on the fact that its 1-*O*-benzyl ether (7; $R^1 = R^2 = CH_2Ph$) was identical (^1H, ^{13}C n.m.r.)[4] to material obtained by the perbenzylation of authentic 2,5-anhydro-D-mannitol[5] (7; $R^1 = R^2 = H$). The crude aldehyde (6) was then converted into 2-(α-D-arabinofuranosyl)maleimide[6] (8), m.p. 134°C, by the six-step procedure developed by Trummlitz and Moffatt[2] for the conversion of (3) into showdomycin (4). The constitution of (8) is firmly based on microanalytical and spectroscopic evidence, and on an X-ray crystal structure determination (Fig. 1a).



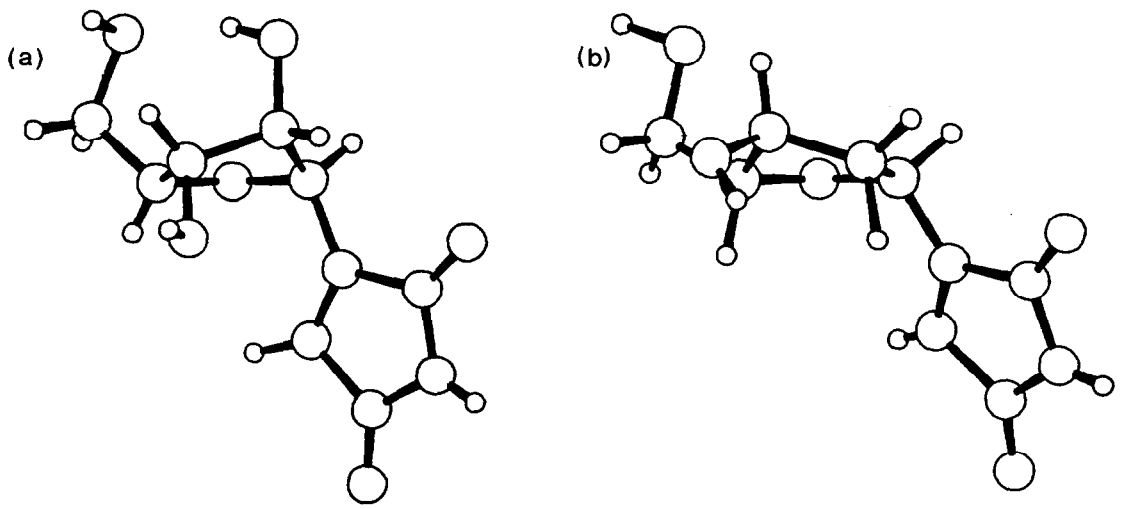
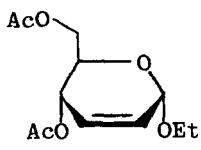
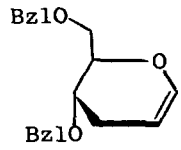


Figure 1. Computer-drawn plots of the molecular structures of (a) 2-(α-D-arabinofuranosyl)-maleimide (8), (b) 2-(α-D-2'-deoxyribofuranosyl)maleimide (12).

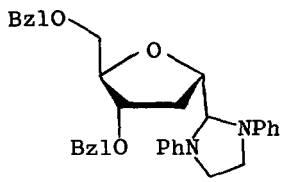
When 4,6-di-*O*-benzyl-3-deoxy-D-glucal (10), which was prepared from (9)[7] in 70% overall yield by a *three-step procedure*[8], was allowed to react with a stoicheiometric quantity of TTN in anhydrous acetonitrile for 30 min at room temperature and the crude products then treated with a slight excess of *N*,*N*'-diphenyl-1,2-ethanediamine in pyridine - acetic acid - water (2:1:1 v/v)[10] solution, (11) was obtained as a crystalline solid, m.p. 47-49°C, in 61% overall yield based on (10). Again, using the procedure developed by Trummlitz and Moffatt[2], (11) was converted into 2-(α-D-2'-deoxyribofuranosyl)-maleimide (12), m.p. 112°C, in 24% overall yield for the seven steps. Like that of (8), the constitution of (12) is firmly based on microanalytical, spectroscopic, and X-ray crystallographic (Fig. 1b) data.



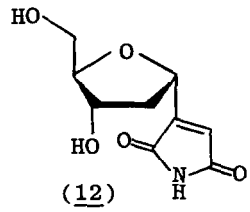
(9)



(10)

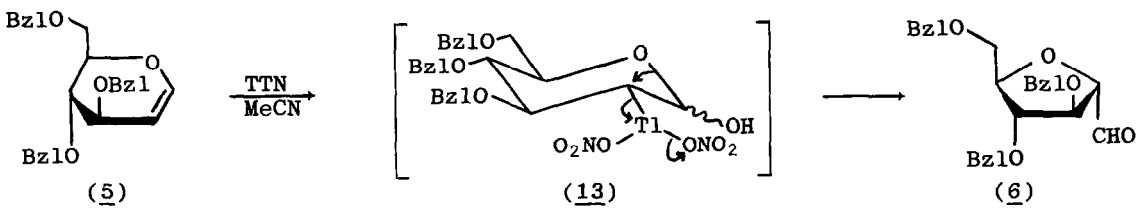


(11)



(12)

Scheme



(5) (13) (6)

The TTN-promoted ring-contraction of (5) leads predominantly to the α-aldehyde (6) [Scheme]. This suggests that (5) undergoes attack by Tl(III) at *C*-2 to give intermediate (13) which then undergoes ring-contraction in the manner indicated. It is reasonable to assume that the TTN-promoted ring-

contraction of (10) involves a 3-deoxy intermediate corresponding to (13). It further seems likely that other glycal derivatives will also prove to be useful starting materials in the preparation of protected anhydro-sugars that are of value in *C*-nucleoside synthesis[11].

Acknowledgement. We thank the S.E.R.C. and Roche Products Ltd for the award of a C.A.S.E. Studentship.

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4 The symmetry of this molecule is revealed by the fact that its ^{13}C n.m.r. spectrum (in $CDCl_3$) contains only three signals (at δ 70.12, 71.71 and 73.27 p.p.m.) assignable to the resonance of methylene carbons and two signals (at δ 81.72 and 84.91 p.p.m.) assignable to the resonance of sp^3-hybridized methine carbons.

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6 3,4,6-Tri-*O*-benzyl-D-glucal (5) was converted into (6) which, in turn, was treated with sodium cyanide and hydrogen peroxide to give[2] a solid mixture of hydroxy-amides, in 55% overall yield. The latter mixture could be converted into (8) in 33% overall yield for the five steps[2]. Before recrystallisation, (8) appeared to be contaminated with *ca.* 5-10% of an impurity which was probably its β-anomer.

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8 The three steps for the conversion of (9) into (10) are: (i) NaOMe/MeOH, 1 hr, RT; (ii) NaH, $PhCH_2Cl$/DMSO, 2.5 hr, RT; (iii)[9] $LiAlH_4$/toluene-tetrahydrofuran, 16 hr, under reflux.

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(Received in UK 21 January 1988)